as originally filed

Livin-specific siRNAs for the treatment of therapy-resistant tumors

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The present invention relates to the use of siRNAs which are specific for the inhibitor of apoptosis protein (IAP) livin (ML-IAP, KIAP) to sensitize tumor cells for apoptosis by down-regulating livin expression. Thus, a novel tool for the treatment of therapy-resistant tumors is provided.

Tumor cells are typically characterized by their failure to undergo so-called programmed cell death or apoptosis, which allows their survival and continuous proliferation under the influence of abnormal growth stimuli. Moreover, apoptosis deficiency is considered to be a major cause for the therapeutic resistance of tumors in the clinic, since many chemo- and radiotherapeutic agents act through induction of apoptosis. An increasing understanding of the regulatory circuits contributing to the apoptosis resistance of cancer cells may therefore provide a rational basis for the development of novel therapeutic strategies, e.g. by specifically interfering with the activity of anti-apoptotic factors in tumor cells. Thus, the problem underlying the present invention refers to the identification of compounds or molecules that specifically modulate distinct steps in the apoptosis pathway by interfering with the activity of anti-apoptotic factors.

Apoptosis pathways involve diverse groups of molecules. One set of mediators implicated in apoptosis are so-called caspases, cysteine proteases that cleave their substrate specifically at aspartate residues. Caspases convey the apoptotic signal in a proteolytic cascade, with caspases cleaving and activating other caspases which subsequently degrade other cellular targets eventually resulting in cellular breakdown. In human tumors, a high expression of anti-apoptotic factors is commonly found and contributes to those neoplastic cell expansion and resistance to the therapeutic action of chemotherapeutic drugs. One group of structurally related proteins with anti-apoptotic properties is the inhibitor of apoptosis protein (IAP) family. IAPs bind to early active caspases, thereby preventing the ongoing of the apoptosis process. They are expressed at high levels in many tumors and, by inhibition of caspases, contribute to the resistance of cancers against apoptosis induction. Examples of IAPs include NAIP, XIAP (hILP), cIAP-1, cIAP-2, BIRC5 (survivin), TIAP, and Apollon. One rather novel member of this family is the livin/ML-